Trends-in-Medicine

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by Lynne Peterson

Quick Pulse

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NEW CLINICAL DRUG EVALUATION UNIT (NCDEU)

Boca Raton, FL
June 13-15, 2006

This annual psychopharmacology meeting, sponsored by the National Institute of Mental Health (NIMH), is usually an excellent venue for reviewing psychopharmacology agents in development, but it was disappointing this year. Many of the posters were repeats of data presented in May 2006 at the American Psychiatric Association meeting in Toronto, Canada, and the lectures tended toward review sessions, providing little insight into drugs in development or issues that are impacting drug development. Even the FDA seminar was disappointing this year, with few messages worth reporting.

Among the most interesting items were:

Alcohol and drug abuse. Dr. Mark Willenbring of the National Institute on Alcohol Abuse and Alcoholism reviewed the links between genes and alcohol and drug abuse. He said, "The neurobiologic basis of alcohol seeking is complicated. The good news is that this gives us a lot of targets, and the bad news is that this gives us a lot of targets. So, it is very unlikely that we'll come up with a single medication or a single modulatory system that is effective."

He pointed out that antidepressants, lithium, traditional antipsychotics, and benzodiazepines do not work for alcohol or drug abuse. Among the drugs he suggested may have potential in this area in the future were:

- Clozaril (clozapine).
- AstraZeneca's Seroquel (quetiapine).
- Johnson & Johnson's Topamax (topiramate).
- Pfizer's Geodon (ziprasidone).
- Sanofi-Aventis's Acomplia (rimonabant).
- Antalarmin, a CRF antagonist.
- NK-1 agonists.
- NPY agonists.

Dr. Willenbring predicted that in 30 years most alcohol dependency will be treated by primary care doctors, adding, "We can't have counselors with a high school education being the primary people dealing with these folks."

Antidepressants. Dr. Mark Zimmerman of Rhode Island Hospital suggested that maintenance studies of antidepressant prophylaxis against recurrence have been incorrectly designed, confusing recurrence and relapses. He explained that maintenance studies are almost always designed as three-phase studies, and continuation trials are mostly placebo-substitution studies. Relapse rates, he said,

should be higher than recurrence rates, but with these trial designs, relapse rates have tended to be comparable to recurrence rates, "This calls into question the distinction currently made between recurrence and relapse that is based on duration of treatment response. We cannot validate that distinction. It is a clear conceptual distinction, but it is based on something we don't know…and we don't know when the underlying biology resolves…I would argue the maintenance studies need to be re-designed…Rather than a three-phase design, they should have a four-phase design:

1. Acute.
2. Responders move on to a continuation phase.
3. Responders move on to a placebo substitution phase (for 2 months) to increase the likelihood that an individual's underlying pathophysiology has resolved.
4. Responders are then entered into a double-blind maintenance phase.

A session on the results of the very large STAR-D depression trial, funded by NIMH, was packed, as attendees sought to better understand the findings of this trial. However, this was primarily a review of previously-released data. STAR-D showed that people whose depression is resistant to initial treatment can achieve remission (absence of symptoms) when treated with a secondary strategy that either augments or switches medications. It was the first study to examine the effectiveness of different treatment strategies for those who did not become symptom-free after initial medication.

Comparison of Zyprexa, Seroquel, and Risperdal

Measurement	Zyprexa n=133	Seroquel n=134	Risperdal n=133
Mean modal dose achieved	11.7 mg/day	506 mg/day	2.4 mg/day
Discontinuations			
Discontinued treatment prior to 1 year	68.4%	70.9%	71.4%
Discontinuations for administrative reasons	3.8%	10.5%	9.8%
Median time to all-cause discontinuation	28 weeks	25 weeks (p=0.751)	25 weeks
PANSS median change from baseline			
At Week 12	-5.2	-4.0 (p<.05)	-5.1
At Week 52	-7.1	-5.3	N/A
Rate of response (≤3 for all PANSS items and ≤3 for the CGI Severity item)	64%	58%	65%
Adverse events			
Most common adverse events	Daytime drowsiness, weight gain, and insomnia	Daytime drowsiness, increased sleep hours, and weight gain	Daytime drowsiness, weight gain, menstrual irregularities
Daytime drowsiness	53.4%	57.5%	49.6%
Weight gain	51.1%	40.3%	41.4%
Insomnia	38.4%	29.1%	33.8%
Increased sleep hours	33.8%	41.8%	27.1%
Menstrual irregularities	31.3%	23.8%	47.1%
Concomitant medications for parkinsonism or akathisia	11%	4%	8%

Anxiolytics. Dr. Murray Stein of the University of California, San Diego, reviewed the use of functional MRI (fMRI) to identify brain areas relevant to anxiety. He suggested that fMRI might answer some or all of these drug development questions:

- Does the drug get into the brain?
- Where does it act?
- Does it generate a profile similar to those of known anxiolytics?
- Is there an indication that you have a new drug?

Atypical antipsychotics. Dr. John Kane of Albert Einstein College of Medicine reviewed the methods for defining and assessing response in antipsychotic clinical trials. He said the percent improvement in total PANSS score is often used but noted that this has problems. He also debunked the idea that antipsychotics take a long time to start working, "The notion that it takes two to three weeks for antipsychotics to work is rather widely held, but, in fact, a good deal of the response occurs in the first and the second week."

Not surprisingly, an AstraZeneca-sponsored study comparing Lilly's Zyprexa (olanzapine), Seroquel, and Johnson & Johnson's Risperdal (risperidone) found they were all equally efficacious, but patients gained more weight with Zyprexa, and Risperdal-treated patients had the greatest increase in prolactin. The primary endpoint was a non-inferiority comparison between Seroquel and Zyprexa and between Seroquel and Risperdal, and Seroquel met this endpoint.

Doctors who were asked about how the CATIE trial has impacted their use of the various atypical antipsychotics all agreed that it has had little or no impact. Zyprexa has side effects, especially weight gain, but it continues to be the most effective agent, they agreed. More than one doctor added, "And that's what CATIE showed." A New England psychiatrist said, "CATIE confirmed my own views on side effects, and it didn't change my use of these drugs."

Weight gain with antipsychotics was investigated in two different posters:

➢ **PFIZER'S Geodon (ziprasidone).** A Pfizer study that reviewed the entire trial database of Geodon (3,507 patients). The study found that Geodon had a weight-neutral profile in both short-term and long-term studies, and they suggested there may be some weight loss long-term with Geodon.

➢ **LILLY'S Zyprexa (olanzapine).** A study by researchers at the University of California, Irvine, which compared weight changes in patients on two formulations of Zyprexa – standard oral therapy and an orally disintegrating tablet (Zyprexa Zydis). They found slightly less – but not significantly less – weight loss with the Zydis formulation. They found patients do gain weight in the first few months of treatment with the orally disintegrating formulation, but they may gain slightly less weight than with conventional Zyprexa.

Bipolar disorder. Dr. Mary Zanarini of Harvard reviewed what she called the first worldwide trials in bipolar disorder – two randomized, double-blind, placebo-controlled, 12-week studies of Zyprexa, one (314 patients) in the U.S. and Western Europe, and the other (451 patients) in the U.S., Latin America, and Eastern Europe. A doctor in the audience said, "The take home message is that this is something you can use…It doesn't make people worse…but it doesn't hurt too much if you stop it."

Black box warnings. Researchers reported on a review of antidepressant prescribing practices in a large managed care plan with ~3.8 million members. They looked at pediatric patient antidepressant prescriptions prior to and after the FDA issued black box warnings in October 2004. They found a significant overall drop in the number of patients taking an antidepressant after the warnings were issued, with the largest overall decrease in younger patients. Among older patients, the largest decrease was in new or first prescriptions. Of 13 specific antidepressants checked, only Lilly's Prozac (fluoxetine), amitriptyline, and trazodone increased in usage; usage of all the others decreased. A researcher said, "Are people getting the message (with black box warnings) that care needs to be taken? I don't know. Preliminarily, I would say yes."

Effect of Black Box Warnings on Pediatric Antidepressant Prescriptions

Measurement	Pre-warning	Post-warning	Change
SSRIs/SNRIs	N/A	N/A	Down 11.9% (p<.0001)
Patients taking antidepressants (*any prescription*)			
All	68,121	61,561	Down 9.7% (p<.0001)
Ages 0-5	466	383	Down 17.8%
Ages 6-9	8,387	7,162	Down 14.6%
Ages 10-14	27,444	24,443	Down 10.9%
Ages 15-17	31,824	29,573	Down 7.1%
Patients taking antidepressants (*new prescriptions*)			
All	N/A	N/A	Down 19.6%
Ages 0-5	355	304	Down 14.4%
Ages 6-9	5,876	5,065	Down 13.8%
Ages 10-14	20,103	16,851	Down 16.2%
Ages 15-17	28,568	21,930	Down 23.2%

Body dysmorphic disorder. Preliminary data presented at NCDEU suggested that serotonin reuptake inhibitors (SSRIs and SNRIs) are effective for treating this disorder. Researchers from Brown University and Weill Medical College of Cornell University studied 185 individuals with body dysmorphic disorder for a mean of 3.0 years. They found that patients treated with a lower-dose SRI – <12 mg/day sertraline; <20 mg/day of Forest Lab's Lexapro (escitalopram); <40 mg/day Prozac, GlaxoSmithKline's Paxil (paroxetine), or citalopram; or <150 mg/day of fluvoxamine or clomipramine – were more likely to report improvement in symptom severity than untreated subjects. The SRI doses were generally within the range often used for depression but lower than recommended for body dysmorphic disorder.

Borderline personality disorder. This is proving a difficult disorder for drug development, in part because there is a huge placebo response. Asked if it is worth it for a company to pursue symptom relief, an FDA official said, "That would be very difficult."

Insomnia. A Sepracor-sponsored, randomized, double-blind, placebo-controlled study found that combining Sepracor's Lunesta (eszopiclone) and Prozac is better than Prozac monotherapy in insomniacs who also have major depressive disorder (MDD). Generally, greater improvements were observed with combination therapy in the more severely depressed patients than in the less severe patients. The message: start combination therapy initially.

Patient reported outcomes (PROs). William Riley PhD of NIMH reviewed the PROMIS trial, which is attempting to develop an internet-based, patient-reported outcomes measure that is publicly available and sustainable – and which the FDA will accept. It is a tailored questionnaire that measures a patient's health status, and it has the potential to provide instant health status reports to patients and healthcare providers to improve treatment decision-making. It is currently in the first wave of testing, with a sample of 12,000 people.

8-Week Results of HAM-D-17 in Patients with Insomnia and MDD Treated with Lunesta + Prozac

Ham-D-17 *(change from baseline)*	Less severe at baseline			More severe at baseline		
	Prozac n=141	Prozac + Lunesta n=136	p-value	Prozac n=127	Prozac + Lunesta n=126	p-value
Total score	-9.9	-11.0	Nss	-13.3	-16.3	0.0007
Total score (excluding insomnia)	-7.5	-7.6	Nss	-10.6	-12.4	0.015
Depressed mood	-1.5	-1.5	Nss	-1.6	-1.8	0.043
Feeling of guilt	-0.8	-1.0	Nss	-1.1	-1.3	0.012
Work and activities	-1.4	-1.5	Nss	-1.4	-1.7	0.014
Agitation	-0.4	-0.2	Nss	-0.5	-0.8	0.046

Issues involved in the fine-tuning of this include:

- Recall period
  - Patient ability to recall the information.
  - If diary recordings are used, ensure that they are done prospectively. ***This is an FDA requirement.***
- Response options
  - Need to be clearly differentiated.
  - Must avoid potential floor and ceiling effects.
  - Can't have a bias in the direction of response.
- Patient understanding needs to be evaluated (cognitive interviews).

Asked if a PRO is likely to be a requirement for every drug approval in five years, perhaps as a primary or co-primary endpoint, Dr. Thomas Laughren, Director of the FDA's Division of Psychiatry Products, responded, "It is hard to say there would be an absolute requirement to have a PRO. The FDA is increasingly interested in looking at things other than symptom domains…and PRO may look at other things like function, and effect on day-to-day life. There have been a couple of situations where we required a measure of function as a co-primary endpoint, and if it turns out that a patient-reported measure is the best way to get to that, it could be a requirement. To say we will absolutely require it is hard to do, but it is a possibility."

FDA and Regulatory Issues

Labeling

The FDA's Dr. Laughren reviewed the new Physician Labeling rule that became final this year. This affects all new NDAs, BLAs, and efficacy supplements – anything that comes in as of 6/3/2006. The FDA also is encouraging companies to reformat labels for older products, but that is not a requirement. ***All*** products must adopt FDA-approved patient labeling by June 30, 2007. This applies to older products, and they can be submitted in the company's annual report to the FDA.

Prior approval of labeling supplements is required, and Dr. Laughren admitted it will be a big burden for the FDA to review these, but he said the FDA is committed to doing it. He also said that the FDA is not expecting companies to do a lot of new data analysis to convert an existing label – in most cases. He added, "We will take this as an opportunity to try to slim down the adverse reaction section because right now I don't think physicians find that section very useful."

Asked if this will prompt companies to do additional work to establish or confirm a drug's mechanism of action in clinical studies, Dr. Laughren said, "The intent is to try to standardize to the extent possible, to find some way of putting a drug into a bin. There are drugs for which we don't know the mechanism. For our indications (psychiatry), that addition to labeling is probably somewhat less valuable.

The last day of NCDEU was also the last day at the FDA for Dr. Paul Andreason, Acting Deputy Director in the FDA's Division of Psychiatry Products (a deputy to Dr. Laughren). He is leaving for a three year stint leading one of the Public Health Service's five 26-person mental health emergency response teams. These teams are a new approach instituted since Hurricane Katrina.

Managing risk

Dr. Andreason discussed managing risk during drug development. He commented, "Every new drug will likely have problems that were not observed in its initial development…There is a risk in being the first (country to approve a drug); your citizens are the population at risk for the rare and yet unknown drug-related serious adverse events…As we develop drugs in the U.S. sooner and faster, which apparently is what people want, there may be things that happen that we don't know about or want. We need to report these things and not be so alarmed about them because this is part of the natural drug development process."

Dr. Alice Hughes, an FDA safety team leader in the Division of Neurology, explained how the FDA makes safety labeling changes, citing the examples of the unique cardiovascular malformation risk in pregnancy with GlaxoSmithKline's Paxil (paroxetine) and process by which Paxil got a label change. Lois Freed PhD, a supervisory pharmacologist with the FDA's Division of Neurology Products, discussed animal toxicology studies, complaining, "We've had a lot of submissions that do not present data in a clear manner, and it seems to be getting worse."

Exploratory INDs

Dr. Freed also explained how Exploratory INDs work, noting that only 5-7 have been issued so far in CDER. She said, "This is fairly new, and people are working through it. Exploratory INDs are designed to facilitate early drug and biologic product development while maintaining subject/patient protection consistent with regulatory requirements. Exploratory INDs provide a flexible approach involving very limited human exposure for a first-in-human trial (excluding children or pregnant or lactating women), allow the use of microdoses and reduced clinical data. Following completion of a clinical trial, the Exploratory IND is supposed to be withdrawn and a traditional IND obtained.

Rating scales. Dr. Andreason said the FDA generally will accept whatever rating scale the "greater academic" community accepts and doesn't like to sign on to a new scale for the benefit of one company.

Asked about reimbursement for pharmacogenomic testing, Dr. Shiew-Mei Huang from the FDA's Office of Clinical Pharmacology and Biopharmaceutics said, "Last year, we (FDA) met with CMS, mostly to provide them with information…They wanted to know how we put the pharma-

cogenomic testing into the label…We don't have the mandate to say these need to be reimbursed…but my understanding is that it is how we put it in our language (that will affect CMS reimbursement)…If we put an adverse event warning – for example, that there is a high risk of Torsade de pointes – I don't think they would dispute coverage…If we have compelling information in the label that links pharmacogenomic information to the use of the drug, I don't see how they can refuse coverage."

Asked if there will be new standards on what adverse events must be listed in a label, Dr. Laughren said, "There should be some reasonable belief in the causality to even list it. That is fairly different than the standards usually applied to the long laundry list of events that go into the adverse event section (of a drug label) and which are probably there more for liability reasons than to help clinicians. This strikes me as an opportunity to try to fix that. Physicians say they don't find the (current) adverse event section very useful and that they tend to ignore adverse event (labeling) because it is filled with table after table, indication after indication – a horrendously long list of other events. Often, these are qualified by saying we have no idea if these are related to the drug. It is a real challenge to try to do this (reduce the adverse event list) because it means making a judgment about a particular event, to determine whether it is related. Is there any reason to list events that occur at the same rate as placebo? Or even less common than placebo? There is absolutely no reason to do that unless there are compelling concerns with challenge, rechallenge, or dechallenge that make you think it might be drug-related. I think more adverse events – at least for psychiatric drugs – are probably not drug-related and most people know that."

Asked if there should be more formal post-market surveillance, Dr. Laughren said that is one answer, but he added, "I can't advocate for changes. There is not a lot of money to do them (FDA-initiated post-market studies), so it depends on drug company willingness to do those studies. I can't advocate (mandating them)."

Specific Drugs

Bristol-Myers Squibb's Abilify (aripiprazole)

A study by researchers at Massachusetts General Hospital in Boston looked at the combination of Abilify and Forest's Lexapro in psychotic major depressive disorder (MDD). MDD affects from 0.6%-1.0% of the population, making it as common as schizophrenia but far less studied, perhaps because it was not thought to be a distinct illness in and of itself, though other studies now indicate it is. The response to tricyclic antidepressants (TCAs) is about 40%, but only 19% with atypical antipsychotics. This combination of Abilify and Lexapro is the fourth study of an atypical antipsychotic plus an SSRI; the other studies were combinations of Zyprexa and Prozac. This study (along with the previous studies) confirms what has become standard practice, and the researcher said, "The results are very similar for Abilify + Lexapro and Zyprexa + Prozac, but the combination of Abilify + Lexapro is very weight neutral, while 25% of patients had weight gain with Zyprexa + Prozac.

Cephalon's Sparlon (modafinil)

There were no new data on this at NCDEU. In March 2006, an FDA advisory committee unanimously recommended against approval of Sparlon for ADHD, recommending the FDA require a large safety trial before approval. A researcher said the company is planning a new trial that will probably start in the fall when children go back to school.

Corcept's Corlux (mifepristone, RU-486)

A rat study looked at the use of mifepristone, which is being developed to treat psychotic depression (at a dose of 600 mg/day for 1 week), as a way to combat the weight gain associated with Zyprexa. The study found that this strategy appears to work. Food consumption was lower, the Zyprexa weight gain was reversed, and concurrent administration with Zyprexa prevented Zyprexa-induced weight gain. However, a company researcher said there are no plans to develop mifepristone for this. Rather, the company has some backup compounds that may have this same effect – without being abortifacients. He said animal toxicology studies are not complete yet, but the company hopes to have one of these in the clinic in a year or two.

Jazz Pharmaceuticals' Zyrem (sodium oxybate)

Researchers from Duke University and the University of Texas Health Science Center at San Antonio presented a proof-of-principle study, funded by Jazz, looking at the efficacy and safety of Zyrem in fibromyalgia. This was the same data presented at the American Psychiatric Association

Review of Data on Zyrem in Fibromyalgia

Measurement	4.5 mg Zyrem n=58	6.0 mg Zyrem n=66	Placebo n=64
Efficacy			
VAS	p<.05	p<.05	N/A
Fibromyalgia Impact Questionnaire (FIQ) score	p<.01	p<.05	N/A
Composite endpoint	p=0.005	p<.05	N/A
Composite endpoint: number of 20% responders	53.4%	53%	26.6%
Clinical Global Impression of Change	p=0.05	p=0.01	N/A
Functional outcomes of sleep questionnaire	~14 (p=0.01)	~14 (p=0.04)	~12.5
SF-36	p<.05	Nss	N/A
Safety			
Nervous system disorders	16	27	10
Psychiatric disorders	12	13	6

meeting. A researcher said the FDA wants an acute trial with six-month data, but that FIQ is accepted by the FDA as a reasonable primary endpoint in fibromyalgia.

JOHNSON & JOHNSON'S paliperidone

There were several posters on this follow-on atypical antipsychotic to Risperdal. It is being developed as both a once-daily oral and a once-monthly injection. Phase III trials are completed, and the oral formulation was submitted to the FDA in November 2005. Phase III trials of the injectable version are not complete.

The only new data on paliperidone were on the hepatic clearance of the oral immediate-release (IR) formulation. A researcher said that study found that paliperidone is unchanged by the kidneys, so it is unlikely to have significant drug-drug interaction, especially with SSRIs. Paliperidone bypasses most hepatic metabolism, which she said would be useful in patients on other drugs or who are hepatically vulnerable or impaired.

In the PK study, 10 patients with moderate hepatic impairment were compared to 10 healthy subjects, and all received 1 mg paliperidone. Hepatically impaired subjects achieved lower total plasma concentrations than healthy subjects, but after correction for the difference in unbound fraction, the exposure was comparable. Researchers concluded that no dose adjustment is necessary in patients with hepatic impairment.

Effects of Hepatic Impairment on PK of Paliperidone IR

Measurement	Healthy subjects n=10	Hepatically impaired subjects n=10
C_{max}	7.14 ng/mL	4.57 ng/mL
T_{max}	~1 hour	
$T_{1/2}$	23.6 hours	26.5 hours
AUC	176 ng·h/mL	128 ng·h/mL
% of dose renally excreted	50.1%	44.7%
Unbound plasma protein fraction	28%	35%
C_{maxu}	1.81 ng/mL	1.59 ng/mL
Creatinine clearance	112 mL/min.	113 mL/min.
Dose excreted unchanged into urine over 96 hours	~50%	~50%
Adverse events		
Hyperprolactinemia	>1 patient	>1 patient
Dizziness	0	2 patients
Deaths	0	0
Discontinuations for adverse events	0	0

Other than fewer drug-drug interactions, the key differences between paliperidone and Risperdal are:

- Paliperidone is a true once-daily, so it has **fewer peaks and troughs**. A researcher explained that ~10% of Caucasians (and more in other ethnic groups) have a polymorphism that makes them poor metabolizers of Risperdal and increases the risk of drug-drug interactions.
- **No titration** is necessary with paliperidone; patients can be started immediately on the optimal dose.
- **Weight gain may plateau** after about six weeks with paliperidone. Data will be presented at the Collegium Internationale Neuro-Psychopharmacologium (CINP) meeting in Chicago in July 2006 on recurrence prevention and weight gain from a double-blind trial. A researcher said, "My interpretation of that data is that there is initial, modest weight gain (~1.8 kg at 3 months), but it looks like it plateaus, and it comes off when the drug is stopped."

Doctors asked about the data said they were not impressed. One commented, "There is no real advantage to paliperidone over risperidone. Hepatic metabolism and titration are not really issues with risperidone. Paliperidone is just a patent protection move. IM (intramuscular) paliperidone would be a good replacement for Risperdal Consta (because it is once monthly and Risperdal Consta is once every two weeks), but there are better (antipsychotic) drugs to watch." He cited three drugs for which there were no data at NCDEU:

- **Pfizer's asenapine.** An expert said, "I'd like to try this in psychotic MDD."
- **Vanda Pharmaceuticals' iloperidone**.
- **Wyeth/Solvay/Lundbeck's bifeprunox**.

NEUROCRINE BIOSCIENCES/PFIZER'S indiplon

No new data on this insomnia treatment were presented at NCDEU either by Neurocrine or by Pfizer, but Pfizer researchers had several posters that rehashed data presented at the American Psychiatric Association meeting in May 2006.

Pfizer researchers offered no insight into the issues the FDA has with the drug. The FDA issued an approvable letter for the 5 mg and 10 mg immediate-release formulations and a not approvable letter for the 15 mg sustained-release formulation. The day after NCDEU, Neurocrine said the FDA wants additional safety data and that final approval of ***any*** dose may require new clinical trials. Neurocrine also said that the FDA questioned the data on the 15 mg SR dose because most of the studies were conducted with doses higher than that.

On June 23, 2006, Pfizer announced it was terminating its agreement with Neurocrine to develop indiplon because of regulatory delays. Neurocrine will get all rights to the drug back, but Pfizer said it will continue to support the project for another 180 days "to ensure a smooth transition."

Currently, no insomnia medication has an indication for depression with insomnia, but there is high comorbidity of these two conditions. A source said insomnia is often followed by depression, and anxiety is often followed by insomnia. Pfizer sources said only two indiplon trials currently are ongoing in depression:

1. A small PK/PD comparison with Lunesta.

2. An 8-week trial designed to show that indiplon rapidly decreases depression in insomniacs with depression.

New River Pharmaceuticals/Shire Pharmaceuticals' lisdexamfetamine (LDX, NRP-104)

Psychostimulant medications, specifically amphetamines and methylphenidate, are considered first-line treatments for ADHD, but amphetamines and methylphenidate are classified as Schedule II substances by the DEA because of the potential for abuse, diversion, and overdose toxicity. New River Pharmaceuticals and Shire are developing an oral powder capsule of lisdexamfetamine, a prodrug of *d*-amphetamine. Lisdexamfetamine was designed to have comparable efficacy to currently-marketed extended-release stimulants but with reduced potential for abuse, diversion, and overdose toxicity. The drug (at doses of 30 mg, 50 mg, and 70 mg) was submitted to the FDA for approval in December 2005 for ADHD.

A PK study found that once-daily dosing of lisdexamfetamine 70 mg was well tolerated in 12 healthy adult volunteers, and the observed adverse events were consistent with those of available amphetamine products. This was a 7-day, open-label, multiple dose study. Steady state was achieved by Day 5, and intact lisdexamfetamine was completely eliminated 6 hours after the final Day 7 dose.

A second PK study in rats looked at oral, IV, and intranasal formulations to see if they could be converted to abusable amphetamine. Researchers found that lisdexamfetamine may have less abuse potential than other amphetamines. Regardless of whether lisdexamfetamine was given intranasally, orally, or by IV, the amount of *d*-amphetamine that can be delivered with lisdexamfetamine is far below other amphetamines. Researchers suggested that the capacity for clearance of amphetamine becomes saturated when the source is *d*-amphetamine sulfate but not when the source is lisdexamfetamine.

PK Studies of Lisdexamfetamine

Measurement	*d*-amphetamine	Lisdexamfetamine
Healthy volunteers		
C_{max}	90.1 ng/mL	47.9 ng/mL
T_{max}	3.7 hours	1.1 hours
AUC_{0-24}	1113.0 ng·h/mL	60.7 ng·h/mL
$T_{1/2}$	10.1 hours	0.4 hours
Rats – intranasal administration		
C_{max}	1962.9 ng/mL	78.6 ng/mL
T_{max}	0.083 hours	1 hour
$AUC_{0-\infty}$	7291 ng·h/mL	91 ng·h/mL
Rats – IV bolus		
C_{max}	420.2 ng/mL	99.5 ng/mL
T_{max}	0.083 hours	0.5 hours
$AUC_{0-\infty}$	546.7 ng·h/mL	237.8 ng·h/mL

Pfizer

➢ **Geodon (ziprasidone), an atypical antipsychotic.** The first pooled analysis looking at weight gain across all the Geodon studies was presented. Researchers reported that they found Geodon to have an overall weight neutral profile – and even a suggestion of weight loss at one year.

➢ **Lyrica (pregabalin), for generalized anxiety disorder (GAD).** A poster showed sustained efficacy with Lyrica in GAD, reinforcing the short-term results. The FDA issued a not approvable letter for Lyrica in GAD, and weight gain has been a concern, but there was little discussion of either of these issues at NCDEU. However, a researcher said, "A lot of people have stopped by (the poster) to say they are using it off-label with very good results." She said the company has another trial underway and plans to resubmit Lyrica in GAD to the FDA.

Predix's PRX-00023, for GAD

A 28-day, single-blind, placebo-controlled, run-in, open-label, forced titration Phase II study in 21 patients raised hopes that the ongoing placebo-controlled Phase III trial will be positive. The most common adverse events were upper respiratory infections (cold/flu, etc.) which occurred in 23.8% of patients at 80 mg and 70.0% at 120 mg.

Phase IIa Results of PRX-00023 in GAD

Measurement	PRX-00023 80 mg	PRX-00023 120 mg
HAM-A (lower is better)		
Baseline	22.9	22.9
Day 14	14.2 (p<.0001)	N/A
Day 28	N/A	12.5 (p<.0001)
Remission rate	32%	

Enrollment in the Phase III trial, which is testing the 80 mg dose, is complete with 310 patients. The primary endpoint is HAM-A total change from baseline. A researcher said it has the "same mechanism of action as buspirone but is a novel class, a serotonin 1A agonist." He admitted the company will need a partner to commercialize this.

Somaxon's doxepin

New data were presented at NCDEU from a 76-patient, randomized, placebo-controlled, crossover, polysomnography (PSG) study evaluating doxepin doses of 1 mg, 3 mg, and 6 mg in elderly adults with insomnia. A researcher reported that there was an immediate effect and it was sustained over 7 hours – "which is unheard of in terms of current drugs." He said the effect peaks at ~1.5 hours, but the onset is "fairly immediate."

Doxepin in Elderly Patients with Primary Insomnia

Measurement	Placebo	1 mg doxepin	3 mg doxepin	6 mg doxepin
PSG results				
Primary endpoint: WTDS (mean)	86.0	70.1 (p=0.0001)	66.4 (p<.001)	60.2 (p<.001)
WASO (mean)	99.0	80.5 (p<.0001)	72.3 (p<.0001)	65.2 (p<.0001)
TST	359.4	376.8 (p<.0001)	388.8 (p<.0001)	397.4 (p<.0001)
LPS	27.1	28.3 (Nss)	23.7 (Nss)	22.4 (Nss)
WTAS	13.0	10.4 (Nss)	5.9 (p=0.026)	5.0 (p=0.008)
Sleep efficiency (SE)	74.9	78.5 (p<.0001)	81.0 (p<.0001)	82.8 (p<.0001)
Subjective sleep parameters				
sWASO	89.6	74.3 (p=0.0297)	72.2 (p=0.0144)	71.5 (p=0.0074)
sTST	339.1	355.7 (p=0.0182)	263.4 (p=0.0005)	369.4 (p<.0001)
LSO	45.8	42.83 (Nss)	42.4 (Nss)	33.9 (p=0.0174)
sNAASO	3.2	3.2 (Nss)	2.9 (Nss)	3.0 (Nss)
Sleep quality	0.5	0.8 (p=0.0357)	0.9 (p=0.0019)	0.8 (p=0.0047)
Adverse events				
Discontinuations	N/A	3 patients		
Any adverse event	10%	12%	8%	7%
Headache	3%	0	0	0

TARGACEPT'S TC-2216, a nicotinic acetylcholine receptor antagonist

Researchers said TC-2216 is potent in reducing immobility in the mouse and rat, and they said it is more potent than classic antidepressants (i.e., desipramine and imipramine). They reported it is equipotent to nicotine in reducing social anxiety in the social interaction test and in increasing the time spent in a mildly aversive environment. TC-2216 exhibits anxiolytic-like activity following acute administration and may also possess anti-obesity properties.

TRANSORAL PHARMACEUTICALS' low-dose transmucosal zolpidem

This is being developed as a treatment for middle-of-the-night insomnia once Sanofi-Aventis's oral Ambien (zolpidem) goes generic in October 2006. The effects are rapid – ~20 minutes vs. ~1 hour for Ambien. A researcher said the 3.5 mg dose is approximately equivalent to 10 mg Ambien, but a 1.75 mg dose is also being developed for people over age 65.

Transmucosal zolpidem (TMZ), TransOral's lead product, is currently in Phase II development, with a Phase III trial planned to start at the end of 2006 or early 2007. The company has not had its end-of-Phase II meeting with the FDA yet. The researcher said the FDA wants:

1. A two-night sleep lab study.
2. A 4-week at-home study.

In a PK/PD trial presented for the first time at NCDEU, transmucosal zolpidem was given to 24 healthy adults in a double-blind, placebo-controlled, 4-way crossover study of 2 consecutive days with morning dosing. Three doses were tested – 1.0 mg, 1.75 mg, and 3.5 mg. The 1.0 mg did not differentiate from placebo on any measure.

Transmucosal Zolpidem (TMZ)

Measurement	Placebo	TMZ 1.0 mg	TMZ 1.75 mg	TMZ 3.5 mg
Change DSST from baseline	N/A	N/A	Down 6.6 (p=0.0132	Down 14.8 (p<.001)
T_{max}	---	36.0 minutes	37.9 minutes	37.9 minutes

TransOral also has a transmucosal sumatriptan for migraine headaches in Phase I development, but this reportedly has had formulation challenges.

WYETH'S desvenlafaxine

There were no new data on this follow-on to Wyeth's Effexor (venlafaxine) at NCDEU. It was submitted to the FDA for approval in December 2005. The key side effect to watch is an increase in blood pressure of 3-4 mm. A researcher said the main – and only significant – advantage of desvenlafaxine over Effexor is less drug-drug interaction because desvenlafaxine is metabolized very little by the liver. ♦